REMARKS

Claims 7, 10, 12-21 are canceled without prejudice or disclaimer. Claims 6 and 24 are amended. Claims 1-6, 8-9, 11 and 22-24 are pending.

It is respectfully submitted that the present amendment presents no new issues or new matter and places this case in condition for allowance. Reconsideration of the application in view of the above amendments and the following remarks is requested.

I. The Rejection of Claims 1-9, 11, 22-24 under 35 U.S.C. 112

Claims 1-9, 11, 22-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The Examiner's reasons underlying the rejection are reproduced below:

> [T]he specification has not disclosed compounds identified by the claimed method from the genomic library. The specification example 1 has not identified peptides or proteins having desired function. The specification disclosure is hypothetical. The specification has not disclosed that the supernatant has at least two secretory products of the microorganism. The specification has not disclosed whether the primary antibodies obtained have mixture of antibodies. The specification description clearly does not provide an adequate representation regarding the open end claimed method of the presently claimed invention.
>
> The specification has not disclosed the antibodies raised in an animal or at least two secreted products present in the supernatants, and then has not shown that the antibody mixture (antibodies to at least 2 supernatant products of microorganism) binds to the cloned genes to identify the secreted compounds of the microorganism. And further if the genomic DNA library is prepared from the organism, the gene that encodes the secretary product may be present or silent, depending on the life phase or time the genomic library is prepared. Thus, the genomic DNA library need to be pre-screened to make sure the genomic DNA library has genes that encode the protein. Thus, using the claimed method at least 2 compounds secreted by the microorganism is not identified. The specification has no support to identify at least 2 secretary products of microorganism using the claimed method.
>
> Further, compounds obtained from the positive clones require further testing or screening to identify the compounds have desired function. Thus, the initial screening may not result in compounds of known function. The specification discloses that bacterial enzymes as the compounds identified by the claimed method, however, none of the working examples show the at least

2 bacterial enzymes identified by the claimed method.

This rejection is respectfully traversed. The present invention is directed to methods for screening for secreted compounds (e.g., enzymes) in which clones producing secreted gene products are identified at the outset so that only these few clones need to be investigated in functional assays to identify proteins of interest. According to the present invention, antibodies are raised against secreted products from a donor microorganism by immunizing an animal with a supernatant obtained by cultivating a microorganism and using the raised antibodies to detect positive clones expressing a cloned gene encoding a secreted compound.

The Examiner alleges that the specification does not disclose that the supernatant will contain secreted proteins stating: "The specification has not disclosed that the supernatant has at least two secretory products of the microorganism." The specification does disclose that the invention is directed to obtaining a supernatant that will contain at least two secretory product. See the specification at page 14. Moreover, such result will inherently follow from the cultivating the microorganism. For example, as exemplified in the specification, the bacterium *B. subtilis* is estimated to produce about 150-1800 extracellular enzymes. See the specification at page 4 citing Hirose et al., Microbiology, 146:65-75 (2000). For fungi, e.g., the number of secreted products is believed to be in the range of about 500-1000 for a given genome. See the specification at page 4. Thus, as would be well understood in the art, such supernatant will contain at least two secretory products. In fact, it is fundamental to existence of microorganisms, such as fungi and bacteria, that secretory proteins are produced, and the scientific literature is exhaustive on this subject. Applicants' statement that microorganisms can secrete at least two compounds is truly beyond dispute in the scientific literature and can not be disputed in this case.

As explained in the specification (see, e.g., page 14-15), after the supernatant is obtained, an animal is then immunized with the supernatant to obtain antibodies for use in screening for positive clones in a subsequent step. Again, the Examiner seems to question a part of the invention which is a scientific principal that is well beyond dispute in the scientific literature. In particular, the Examiner alleges that: "The specification has not disclosed whether the primary antibodies obtained have mixture of antibodies." The specification, however, teaches that the primary antibodies obtained have mixtures of antibodies. See the specification at page 15. Moreover, the production of such antibodies will again inherently result from the immunization of the animal with the supernatant as described and claimed. In such an immunization process, the animal will generate a mixture of antibodies against the at least two secreted compounds (secreted by the microorganism) thereby producing a mixture of antibodies. See Scand. J.

Immnol, Vol. 17, Suppl. 10, pp. 345-351 (1983). Hence, Applicants statement that a mixture of antibodies can be produced is truly beyond doubt and should not be disputed in this case.

Thus, the process of obtaining a mixture of antibodies raised against at least two secreted products by immunizing an animal with a supernatant obtained by cultivating a microorganism is well-described in the specification, and moreover, such processes are accepted in science as fundamental microbiological and immunological technology. It is improper to conclude that Applicants were not in possession of this aspect of the invention. Moreover, the Examples provided in the specification show that applicants were able to obtain a mixture of antibodies raised against the secretory proteins, hence an actual reduction to practice, further evidencing that Applicants were in possession of this aspect of the claimed invention. See Example 4 describing the identification of eighteen clones representing at least eight different molecular weights.

The Examiner also raises doubts as to whether the antibodies raised will then be able to identify the clones in the subsequent process steps. In particular, the Examiner states that: "The specification has not disclosed the antibodies raised in an animal or at least two secreted products present in the supernatants, and then has not shown that the antibody mixture (antibodies to at least 2 supernatant products of microorganism) binds to the cloned genes to identify the secreted compounds of the microorganism." Again, the Examiner appears to be challenging principles of the invention that are so well accepted as to be beyond question, i.e., the reliability of technology underlying immunoassays. The present invention relies (in part) on the same scientific basis supporting the use of antibodies in other immunoassays. See, e.g., WO 89/08114 and Analytic Biochem., Vol. 270 (1) pp. 103-111 (1999) which describes the use of antibodies to identify compounds, such as expression products. Moreover, the examples again show that the Examiner doubts are not valid as Applicants were clearly able to raise a mixture of antibodies against two or more secreted proteins and then identify clones expressing a cloned gene encoding the secreted compounds. Again, see Example 4 describing the identification of eighteen clones representing at least eight different molecular weights.

The Examiner also alleges that the claimed method requires some "pre-screening" to make sure the genomic DNA library has genes that encode the protein. Foremost, the claims also encompass a CDNA library (see the specification at page 12), and the Examiner's allegation is not applicable to this type of gene library. However, with respect to a genomic DNA library, the Examiner's allegation has no merit as to the issue before the Examiner, *whether Applicants specification demonstrates that Applicants were in possession of a method for screening a*

genomic library. The point that some secreted protein in a genomic library may not be present due to the phase or time the library was prepared has absolutely no relevance to whether the written description requirement has been met. The specification teaches that that invention is applicable to both genomic DNA and CDNA libraries. See the specification at page 12 and 16. An artisan may choose to screen a genomic library or a CDNA library, as instructed by the specification. The specification provides an example showing that the invention can be applied to a gene library. The invention is a screening method and the claims do not require identifying every protein which might be encoded in a gene library. Furthermore, although not required, if an artisan wants to pre-screen, the claims do not prevent him or her from doing so.

The Examiner also challenges whether the compounds obtained from the positive clones require further testing or screening and that the initial screening may not result in compounds of known function. Again, it is not clear how the Examiner's statements relate in any way to the issue of whether Applicants have fulfilled the written description requirement of the Patent Code. Applicants' invention is a screening method. As disclosed in the specification, and as recited in the claims, the method can be used to screen for a protein having a desired function. An artisan is not required to engage in further testing or screening, although he or she is certainly permitted to do so as the claims do not restrict this action. Moreover, the Examples show that in one example, eighteen clones, representing at least eight different molecular weights, were identified by the claimed method. See Example 4, page 37. An artisan could then screen these eight products in various activity assays to identify a product of interest, e.g., an assay for alpha-amylase activity if alpha-amylase activity is of interest. If no alpha-amylase is found in the activity screen, this does not mean the invention doesn't work and Applicants were not in possession of such screening method, it simply means that alpha-amylase was not identified in this particular experiment.

For the foregoing reasons, Applicants submit that the claims overcome this rejection under 35 U.S.C. 112. Applicants respectfully request reconsideration and withdrawal of the rejection.

II. The Rejection of Claims 6 and 7 under 35 U.S.C. 112

Claims 6 and 7 are rejected under 35 U.S.C. 112, as indefinite.

Claim 6 is rejected as lacking antecedent basis for "the secreted product." Claim 6 is amended to provide proper antecedent basis.

Claim 7 is rejected has lacking antecedent basis for "the donor organism." Claim 7 is cancelled, rendering the rejection moot.

For the foregoing reasons, Applicants submit that the claims overcome this rejection under 35 U.S.C. 112. Applicants respectfully request reconsideration and withdrawal of the rejection.

III. The Rejection of Claim 24 under 35 U.S.C. 102

Claim 24 is rejected under 35 U.S.C. 102 as anticipated by Rehman.

Rehman was overcome with respect to Claim 1 and dependent claims by amending the claims to clarify that the invention is directed to a method for screening for compounds secreted by a microorganism whereas Rehman et al. relates to proteins from the gut of the nematode *H. contortus*.

Claim 24 is amended to recite a method for screening for compounds secreted by a microorganism and hence is also not anticipated by Rehman.

For the foregoing reasons, Applicants submit that the claims overcome this rejection under 35 U.S.C. 102(b). Applicants respectfully request reconsideration and withdrawal of the rejection.

IV. Conclusion

In view of the above, it is respectfully submitted that all claims are in condition for allowance. Early action to that end is respectfully requested. The Examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this amendment or application.

Respectfully submitted,

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Jason I. Garbell, Reg. No. 44,116
Novozymes North America, Inc.
500 Fifth Avenue, Suite 1600
New York, NY 10110
(212)840-0097